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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/053,530 | 01/17/2002 | Jeffrey A. Ledbetter | 390069.401 | 8993 |
| 7590 | 03/01/2005 | | EXAMINER | |
| Buchanan Ingersoll Professional Corporation One Oxford Center 301 Grant Street Pittsburgh, PA 15219-1410 | | | HELMS, LARRY RONALD | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1642 | |

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|-----------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/053,530 | LEDBETTER ET AL. |
| | Examiner | Art Unit |
| | Larry R. Helms | 1642 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 20 December 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,2,4-13,19 and 23-142 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 23-49,102-106 and 142 is/are allowed.
- 6) Claim(s) 1,2,4-13,19,50-101 and 107-141 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>12/21/04</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

1. Claims 1, 5-7, 35-38, 98 have been amended.
Claims 3, 14-18, 20-22 have been canceled (previously).
2. Claims 1-2, 4-13, 19, 23-142 are pending and under examination.
3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action

Rejections Withdrawn

4. The rejections of claim 12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.
5. The rejection of claims 78, 82, 98 under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) is withdrawn in view of reconsideration. It is noted that the response stated that claims 78 and 82 have been canceled, however, these claims are still pending.
6. The rejection of claims 40-41, 43-48, 54, 99, 101-102 under 112 first paragraph for lacking deposit of the biological material 2H7, HD37, G28-1 is withdrawn in view of the showing of the sequences of the VH and VL are provided in the instant application.
7. The rejection of claims 1-2, 4-13, 19, 23-142 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention is withdrawn in view of the arguments and that the claims can encompass indirectly joined fusions.

8. The rejection of claims 5, 6, 110 under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01) is withdrawn in view of arguments for priority.

9. The rejection of claim 53 under 112 first paragraph is withdrawn in view of the arguments.

10. The rejection of claims 1-2, 4-5, 6-12, 19, 50-51, 55-56, 59, 64-66, 68-69, 72-79, 82, 84-98, 109-113, 117-119, 129-138 under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01) and further in view of Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) and Bodmer et al (U. S. Patent 5,677,425, issued 10/97) is withdrawn in view of arguments.

Response to Arguments

11. The rejections of claims 1-2, 4-11, 13, 19, 50-101, 109-141 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 12/20/04 states that claim 1 has been amended to recite derived from a wild-type human IgA hinge region and claim 6, 7, 139-141 do not have the term derived in them (see page 25-26 of the response). In response to this argument, it is still unclear, even though the claims require a certain number of cysteins

or mutations of the number of cysteines, whether the amino acid sequence of other residues in the hinge is altered and therefore would encompass other IgG, or even IgM hinges.

12. The rejection of claims 52-53 under 112 first paragraph for lacking deposit of the biological material L6, 1F5 is maintained.

The response filed 12/20/04 has been carefully considered but is deemed not to be persuasive. The response states that the heavy and light chain variable regions for the antibodies are either in US Patent 5,354,847 or in ATCC HB8677, 9240 and 9241 for L6 and in Shan Blood 91:1644-1652, 1998 or in ATCC HB-9645 (see pages 27-28 of response). In response to this argument, it is unclear if the antibodies claimed are those described in the ATCC numbers or in the patent or reference. There is nothing in the claims except for lab designations to indicate the antibodies. In addition, it is unclear how three ATCC numbers could be for the L6 antibody when the sequence should be only one ATCC number. Since the claims are to "a" single chain antibody it is unclear if the claims are to other antibodies or only those having a specific sequence in the heavy or light chain and the rejection is maintained and made again.

13. The rejection of claims 107-108 under 112 first paragraph is maintained.

The response filed 12/20/04 has been carefully considered but is deemed not to be persuasive. The response states that the recitation of "any hinge peptide or polypeptide that occurs naturally" is support on page 22 of the specification and this

includes the IgE hinge and cites several case laws for the point (see page 29-30 of response). In response to this argument, there is no support for the limitation of an IgE hinge. The support is comparable to that in Purdue Pharma L.P. V. Faulding Inc. 230 F. 3d 1320 1326, 56USPQ2d 1481, 1486 Fed Cir 2000 and In Re Ruschig 154 USPQ 118 CCPA 1967 which stated that just because one recites a forest of trees does not provide support for a specific tree. The situation is comparable because applicant has stated any hinge peptide and describes several but does not point to the specific IgE hinge. The specification only describes IgG and IgA hinges. This is not persuasive and the rejection is maintained.

14. The rejection of claims 1-2, 4, 7-8, 19, 135-138, under 35 U.S.C. 102(b) as being anticipated by Bodmer et al (U. S. Patent 5,677,425, issued 10/97) is maintained.

The response filed 12/20/04 has been carefully considered but is deemed not to be persuasive. The response states Bodmer is directed to complete antibodies and does not teach binding domain polypeptides coupled to hinges as claimed and Bodmer fails to teach a protein lacking a CH1 domain (see page 34 of response). In response to this argument, Bodmer teach hinges having only one cysteine after mutations of IgG1-4 molecules. As evidenced from Cruse et al, Illustrated Dictionary of Immunology, CRC Press, page 157, 1995, all of these hinges have two or more cysteines which meet the limitations of claim 1(i). In addition, as the response to the 112 second above noted that the claims do encompass indirectly joined polypeptides, the claims do encompass entire antibodies as taught by Bodmer. The response further states that it seems clear that

Bodmer does not anticipate the claims because the Office Action stated that Bodmer appear to have produced antibodies that are identical to the claimed antibody.

However, Applicants are not claiming antibodies as used in Bodmer (see page 34 of response). In response to this argument, the rejection stated that Bodmer did not disclose the properties of the Ka of the affinity claimed in claims 135-136 but it was the examiners position that the antibody fusion protein of Bodmer would have the claimed properties. One of ordinary skill in the art would reasonably conclude that Bodmer's antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Bodmer have produced antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed binding protein with the protein of Bodmer, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed protein and the protein of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Because the claims encompass entire antibodies and has been admitted to encompass indirectly joined binding domains and hinges, the art reads on the claims.

15. The rejection of claims 1-2, 4, 7-8, 12, 19, 129, 135-138 under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01) is maintained.

The response filed 12/20/04 has been carefully considered but is deemed not to be persuasive. The response states that the Gillies published application does not get the 3/01 date because the provisional does not support written description (see pages 34-39 of response). The response states that the Gillies provisional has a preferred embodiment of decreased Fc effector functions and whole antibodies (see page 35). In response to this argument, this may be the preferred embodiments but the provisional also teaches and has support for fusion protein and antibodies with one cysteine in the hinge of a IgG1 hinge (see page 6) and using IgG2-4, IgA hinges (see page 11) and human Fc CH2, CH3 (see page 14). The response states that the Gillies published application does not refer to an IgG1 hinge modified to have one cysteine (see page 37 of response). In response to this argument, as stated above the provisional has support for an IgG1 hinge mutated to have one cysteine and since an IGg1 has only two cysteines the limitation in claim 1(i) is met.

The response states that none of the ten paragraphs contain references to single chain Fvs (see page 37). In response to this argument, claims reciting scFv have been withdrawn from the rejection.

The response further states that Enbrel does not mediate ADCC or complement fixation (see page 38-39 of response). In response to this argument, Enbrel is just an example of a fusion and the provisional provides numerous others as well as the generic concept and the Fc can mediate ADCC or complement and use an IgG1 CH2, CH3 (see pages 14, and page 23, lines 24-25).

Conclusion

16. Claims 23-49, 102-106, 142 are in condition for allowance.
17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms

571-272-0832



LARRY R. HELMS, PH.D
PRIMARY EXAMINER